Review

Shades of gray: the world of quantitative disease resistance

Jesse A. Poland[1], Peter J. Balint-Kurti[2], Randall J. Wisser[3,4], Richard C. Pratt[5] and Rebecca J. Nelson[1,6]

[1] Department of Plant Breeding & Genetics, Cornell University, Ithaca, NY 14853, USA
[2] USDA-ARS, Plant Science Research Unit, Department of Plant Pathology, North Carolina State University, Raleigh, NC 27695, USA
[3] Department of Plant Pathology, North Carolina State University, Raleigh, NC 27695, USA
[4] Current address: Department of Plant and Soil Sciences, University of Delaware, Newark, DE 19716, USA
[5] Department of Horticulture and Crop Science, The Ohio State University, Wooster, OH 44691, USA
[6] Department of Plant Pathology & Plant-Microbe Biology, Cornell University, Ithaca, NY 14853, USA

A thorough understanding of quantitative disease resistance (QDR) would contribute to the design and deployment of durably resistant crop cultivars. However, the molecular mechanisms that control QDR remain poorly understood, largely due to the incomplete and inconsistent nature of the resistance phenotype, which is usually conditioned by many loci of small effect. Here, we discuss recent advances in research on QDR. Based on inferences from analyses of the defense response and from the few isolated QDR genes, we suggest several plausible hypotheses for a range of mechanisms underlying QDR. We propose that a new generation of genetic resources, complemented by careful phenotypic analysis, will produce a deeper understanding of plant defense and more effective utilization of natural resistance alleles.

The two worlds of disease resistance

Two general categories of disease resistance have long been recognized in plants (e.g. Ref. [1]): (i) complete resistance conditioned by a single gene and (ii) incomplete resistance conditioned by multiple genes of partial effect. In their extreme forms, these types of resistance are clear and easily distinguished. A variety of terms have been used to refer to this perceived dichotomy, including horizontal versus vertical, complete versus incomplete, major-gene versus minor-gene and narrow-spectrum versus broad-spectrum. This diversity of terms reflects the range of interests and assumptions made by the respective authors, but it also adds an element of confusion to the literature because some terms are used in different ways by different authors. Here, we use the terms 'qualitative disease resistance' and 'quantitative disease resistance' (QDR; see Glossary) to refer to the respective phenomena. We use the term 'R-genes' (resistance genes) to refer to genes that confer qualitative effects and 'QRLs' (quantitative resistance loci; see Glossary) [2] to refer to loci or genes that confer QDR. Although the phenomena of qualitative and quantitative resistance can be considered different, there is a great deal of gray area between the extremes, suggesting that it might be useful to reexamine the concepts in light of emerging evidence on mechanisms of resistance. As we will discuss, several authors have questioned whether the loci controlling the two types of resistance are distinct [3], suggesting that quantitative and qualitative resistance are conditioned by the same genetic mechanisms.

There is substantial support for this hypothesis in some cases, as well as evidence that alternative mechanisms also underlie QDR (e.g. Refs [4,5]). Several credible hypotheses can be proposed, and it is likely that a diversity of mechanisms will be implicated, some overlapping with qualitative resistance (e.g. specific recognition of pathogen effectors or their targets) and innate immunity (e.g. relatively non-specific recognition, such as recognition of broadly conserved pathogen features; also known as basal resistance). Other plausible mechanisms to explain QDR would include the detection and mitigation of infection-related damage, the modulation and transduction of defense signals and mechanisms of direct defense (e.g. establishment or reinforcement of defensive structures,

Glossary

Compatible interaction: a host–pathogen interaction that results in disease (the host is susceptible).
Defeated R-gene: a resistance gene that has become ineffective.
Incompatible interaction: a host–pathogen interaction that does not result in disease (the host is resistant).
NB-LRR (nucleotide binding-leucine rich repeat): two amino acid sequence motifs commonly found in resistance genes.
Near isogenic lines (NIL): inbred lines that differ at only a small genomic region.
Pathosystem: the combination of a specific host species and pathogen species.
Pattern-recognition receptors: proteins that identify molecules, such as flagellin or chitin components, that are associated with microbial pathogens.
Quantitative disease resistance (QDR): resistance that is expressed as a reduction in disease, rather than as the absence of disease.
Quantitative resistance locus (QRL): a locus with an effect on QDR.
Quantitative trait locus (QTL): a locus with an effect on a quantitative trait (i.e. a trait showing continuous variation).
Recombinant inbred line (RIL): an inbred line produced from an initial cross followed by continuous inbreeding; populations of RILs are often used for QTL-mapping studies.
Resistance breakdown: the phenomenon of a resistant cultivar becoming susceptible owing to changes in the pathogen race.
Resistance gene analogs: putative genes that share sequence similarity with known R-genes.
R-gene breakdown: the phenomenon of a resistance gene becoming ineffective in a crop variety.

Corresponding author: Nelson, R.J. (rjn7@cornell.edu).

1360-1385/$ – see front matter doi:10.1016/j.tplants.2008.10.006 Available online 4 December 2008

antimicrobial secondary metabolites or detoxification of pathogen-derived toxins). The mechanisms involved in conditioning QDR are likely to have implications for resistance spectra and durability associated with specific QRLs. Mechanisms of specific recognition might eventually be overcome as a result of pathogen evolution, whereas non-specific defense mechanisms could provide resistance that is relatively broad in spectrum and robust in the face of pathogen evolution.

Although various authors have speculated on the types of gene that might underlie QRLs, the evidence to date has often relied on colocalization of QRLs and genes in low-resolution mapping studies [6,7]. In this situation, limited inference can be made because hundreds of genes are typically located in genomic regions defined by QRLs. In some cases, however, positional cloning has been achieved, and it is expected that more QRLs will be isolated in the near future. Here, we synthesize and interpret the literature pertaining to the mechanisms of QDR in plants, focusing primarily on fungal pathosystems but with some reference to bacterial systems. Viral systems are not considered because the pathogenic strategies of viruses are so different from those of fungi and bacteria. We provide a brief overview of qualitative and quantitative resistance, assess recent developments in understanding QDR in crop and model species, place these findings in the context of the broader understanding of plant defense and suggest ways in which greater synergies could be achieved.

The limitations of qualitative resistance

R-genes typically provide high levels of resistance and are relatively easy to manipulate, both in basic research and applied breeding programs. These genes are important in many systems, but their utility varies among pathosystems (see Glossary) and among genes within a pathosystem. The primary limitations of R-genes for crop protection are (i) a lack of durability in some systems (primarily with respect to pathogens that have high evolutionary potential [8]) and (ii) a lack of availability in others (primarily necrotrophic systems).

The ephemeral nature of R-gene-mediated resistance is highlighted by a recent outbreak of a new strain of wheat stem rust (caused by *Puccinia graminis* race Ug99) that is virulent on cultivars carrying widely deployed R-genes [9]. The deployment and breakdown of R-genes (see Glossary) for diseases such as wheat rust has entailed a frustrating battle for plant breeders, pathologists and farmers, and more durable resistance is needed [10]. In potato (*Solanum tuberosum*), most lines that chiefly rely on R-gene-mediated resistance have been rapidly overcome by virulent populations of *Phytophthora infestans*, which causes potato late blight. In addition to subjecting pathogen populations to high levels of selection pressure, the presence of R-genes shifts the trait distribution in such a way that underlying QRLs cannot be detected. This phenomenon has led to the intentional elimination of R-genes in some breeding programs so that QDR can be more effectively assessed and advanced [11].

Several recent reviews have discussed current insights into R-gene-mediated resistance [12–14]. Many R-genes have been isolated and characterized, and the downstream responses that they trigger are increasingly well understood. R-genes typically encode proteins that recognize pathogen effectors or modifications of plant proteins that are targets of those effectors [13]. Among the six classes of R-genes, the most common class contains characteristic nucleotide binding-leucine rich repeat (NB-LRR; see Glossary) amino acid sequence motifs involved in recognition and related functions. However, other mechanisms have been associated with qualitative resistance, including detoxification of fungal toxins (e.g. *Hm1* and *Hm2* in maize [*Zea mays* ssp. *mays*] [15]), modulation of the defense response (e.g. *mlo* in barley [*Hordeum vulgare*] [16]) and transcriptional regulation (e.g. *Bs3* in pepper [*Capsicum annuum*] [17]).

On invasion by biotrophic pathogens, R-genes mediate a highly effective defense response; this usually involves a hypersensitive response (HR) in which tissue immediately adjacent to the site of pathogen ingress undergoes rapid programmed cell death. However, the same response can increase susceptibility to necrotrophic pathogens. For a pathogen that thrives on dead host tissue, exploiting programmed cell death in the host is a perfect method for acquiring nutrients. This is illustrated in two studies showing that necrotrophic pathogens can produce host-specific toxins that activate R-gene-mediated defense responses, resulting in host cell death ([18,19], J. Bennetzen, personal communication). Thus, it is not surprising that R-gene-mediated defense to necrotrophic pathogens is rare. The few known naturally occurring qualitative resistance genes for true necrotrophs encode detoxification enzymes rather than genes that mediate the HR (e.g. Refs [15,20,21]). However, quantitative genetic resistance to necrotrophic pathogens is typically available and can be effective (Figure 1; e.g. Ref. [22]).

What is QDR, and why should we care about it?

QRLs have been identified in most plant pathosystems studied to date. As of mid-2008, we identified from the literature 25 QRL-mapping studies for rice (*Oryza sativa*) diseases, 43 for maize diseases and 13 for *Arabidopsis* (http://www.plantpath.cornell.edu/Labs/Nelson_R/TIPS2008_QRLcitations.html). The large number of studies on crop species reflects the importance of QDR in agricultural production. QDR has been reported in several *Arabidopsis* pathosystems, including *Pseudomonas syringae* [23], *Erysiphe cichoracearum* [24] and *Botrytis cinerea* [25]. Variation in QDR is important for crop improvement and can be selected, often leading to high levels of phenotypic resistance [26]. For some plant diseases, such as rice blast and bacterial blight, resistance breeding relies on a combination of quantitative and qualitative forms of resistance. For other diseases, including those caused by necrotrophic pathogens, QDR is the most important or only form of resistance available (Figure 1).

Observations of the performance of crop cultivars with different types of resistance have led to the conclusion that QDR tends to be more durable than typical R-gene-mediated resistance [27]. Whereas R-genes can be rapidly overcome as a result of strong selection for compatible pathogen variants, resistance breakdown (see Glossary) is considered to be less of a problem with QRLs because of

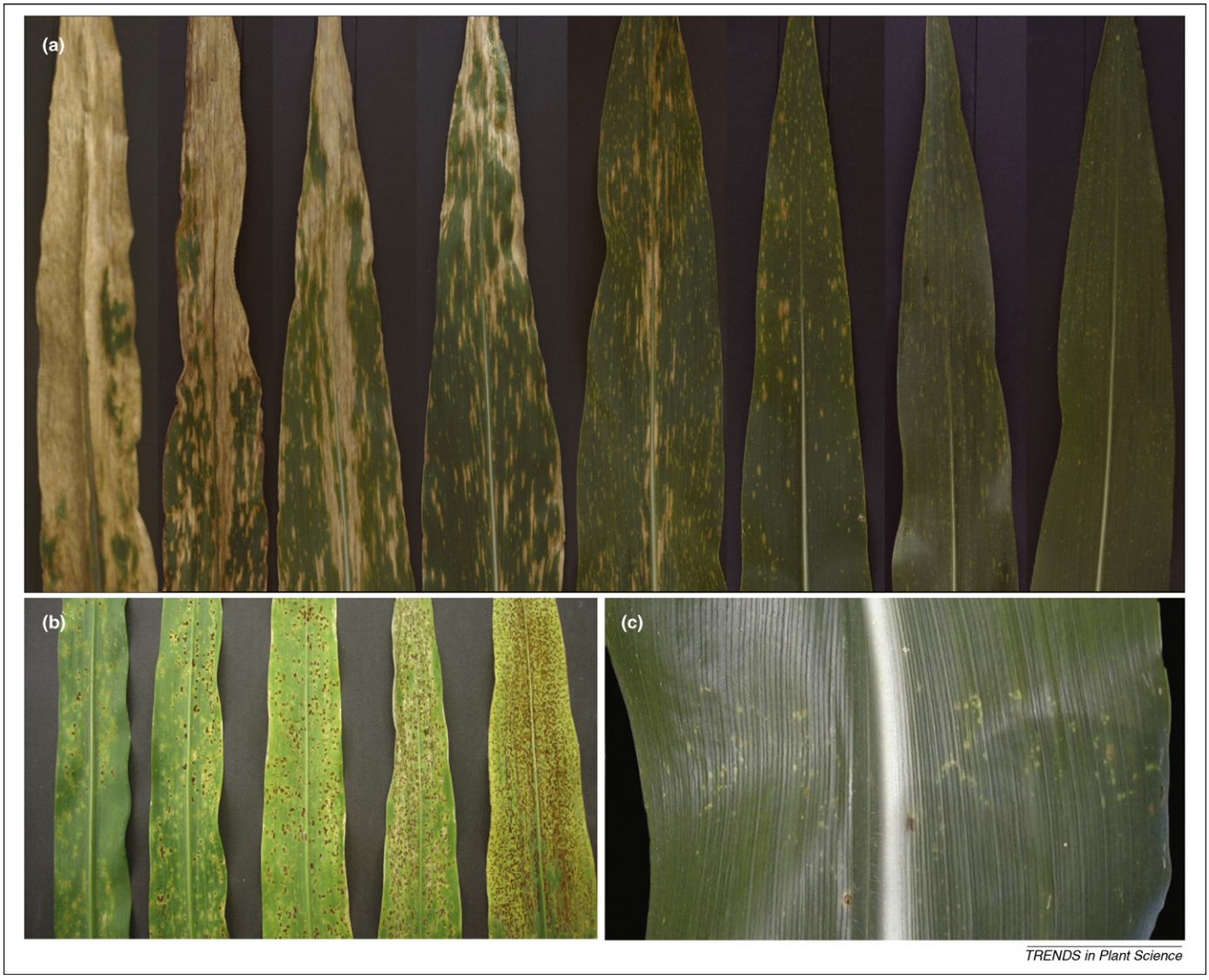

Figure 1. Examples of quantitative disease resistance (QDR) in maize. **(a)** Quantitative variation for resistance to *Cochliobolus heterostrophus,* the causal agent of southern leaf blight, in a segregating maize population. Each leaf is representative of a recombinant inbred line derived from a cross between maize inbred lines B73 and De811. The range of differences in levels of foliar blight indicates that there is large variation in QDR for this pathogen. This QDR can be effective, even though R-genes are not present for resistance to *C. heterostrophus*. **(b)** Range in QDR to *Puccinia sorghi* in a segregating maize population in contrast to **(c)**, which shows a hypersensitive resistance reaction from the R-gene *Rp1*. Although the resistance provided by R-genes is highly effective, it is often subject to breakdown resulting from pathogen evolution. Reproduced with permission from Chi-ren Shyu and Jason Green (a); Jesse Poland (b); and Jerald Pataky (c).

their smaller effects (leading to lower selection pressure on the pathogen) and/or presumed broader specificity (the latter being widely assumed but little documented). Because QDR is controlled by multiple genes with partial and inconsistent effects, pathogen variants that overcome QRLs gain only a marginal advantage.

QDR in context of the current model of plant–pathogen interactions

Jones and Dangl [14] recently summarized the complex interplay between (biotrophic) pathogen attack and host defense as a multi-phase 'zig-zag' process, in which the evolutionary arms race between host and pathogen results in an oscillation between compatible (susceptible) and incompatible (resistant) states over time (see Glossary). The host plant initially recognizes features common to many microbes, such as flagellin or chitin (microbial- or pathogen-associated molecular patterns [MAMPs]) using pattern-recognition receptors (see Glossary). This recognition event then triggers the innate immune response (also known as host basal defenses) to arrest further pathogen development (i.e. MAMP-triggered immunity). Successful pathogens evade basal defenses, such as cell wall apposition, using effector proteins that disrupt the normal defense response. In turn, host plants have evolved NB-LRR proteins that recognize these pathogen effectors and mount heightened defense responses (i.e. effector-triggered immunity). The loss or mutation of specific pathogen effector proteins enables avoidance of R-gene recognition and virulence. R-gene recognition and corresponding losses and mutations of effectors (products of avirulence genes) leads to the widely recognized 'gene-for-gene' interactions. This type of interaction is typified by a strong resistance or susceptibility phenotype, but modifier loci can affect the strength of R-gene-mediated defense (e.g. Refs [28,29]). Because there are multiple

genes involved in the resistance pathway, natural functional mutations could introduce quantitative variation to several or all of the phases described in the zig-zag model, adding shades of gray to the extremes of complete resistance and susceptibility. Nonetheless, it is unlikely that this model accounts for all known forms of QDR, and it has been primarily constructed based on observations of biotrophic pathogens for which R-gene-mediated recognition and defense is effective.

Mechanisms underlying QRLs: hypotheses, credibility, evidence and proof

As an increasingly broad range of microbial pathogenic strategies and a corresponding range of host defense strategies are recognized, a corresponding array of molecular mechanisms can be postulated as playing a part in QDR. We highlight several hypotheses below and outline evidence pertaining to each. Even at this early stage it is clear that more than one hypothesis is likely to be valid and that no single hypothesis can fully explain the breadth of QDR. It is likely that future work will suggest additional hypotheses and mechanisms.

Hypothesis #1. QDR is conditioned by genes regulating morphological and developmental phenotypes

Plant diseases develop within the spatiotemporal context of plant development, so it is reasonable to speculate that some QRLs are based on genes that control plant architecture or development. It has been well documented in many necrotrophic plant–pathogen systems that flowering time is strongly correlated with disease resistance, such that susceptibility is apparently enhanced after flowering (e.g. Ref. [30]). Other developmental-stage-specific QRLs have been documented [31,32]. Morphological traits, such as stomatal density and/or openness or the ability to repel water can have important effects on disease resistance [33,34], in addition to other aspects of plant morphology, such as plant height, leaf area and leaf angle [35,36]. Therefore, it is likely that genes affecting growth and development, as well as plant architecture, have pleiotropic effects on disease resistance.

Hypothesis #2. QRLs represent mutations or different alleles of genes involved in basal defense

Flagellin (the main constituent of bacterial flagella) and chitin (the main component of fungal cell walls) are two widely conserved pathogen features that enable plants to recognize broad pathogen groups. Work with the *Arabidopsis* gene *FLAGELLIN-SENSITIVE 2* (*FLS2*), an LRR-receptor-like kinase (RLK) involved in the perception of flagellin, has established a mechanistic basis of flagellin recognition and basal resistance in plants [37]. Mutations in *FLS2* seem to produce a phenotype of modest (quantitative) effects on disease severity and bacterial colonization when tested under natural conditions [37], and different alleles of *FLS2* have been found in several *Brassica* species [38]. Thus, allelic variation at *FLS2* might be considered a QRL in a segregating population.

Fungal chitin also triggers basal resistance [39]. The host RLK, *chitin elicitor receptor kinase 1* (*CERK1*, also called *LysM RLK1*), is involved in chitin perception and defense signal transduction. Mutations in *CERK1* conditioned reduced resistance to the normally incompatible necrotrophic fungus *Alternaria brassicicola* [40] and quantitative differences in resistance to the biotrophic fungal pathogen *Erysiphe cichoracearum* but did not affect resistance to the bacterial pathogen *Pseudomonas syringea* [41,42]. Thus, it seems probable that similar mutations or allelic changes might underlie QRLs for fungal pathogens. These examples support the hypothesis that pattern-recognition receptors acting in basal defense can condition quantitative differences in the resistance phenotype. The recognition of conserved pathogen features, such as flagellin or chitin, could also explain the broad spectrum resistance of some QRLs (Box 1).

Hypothesis #3. QRLs are components of chemical warfare

Pathogen-produced phytotoxins have long been recognized as important compounds in promoting plant disease. The enzymes that detoxify them are recognized as important plant defenses, as are the 'antibiotics' (phytoalexins) that

Box 1. Broad-spectrum QRLs: evidence for multiple disease resistance

In both natural and agricultural systems, plants are exposed to taxomically diverse pathogens, including fungi, bacteria, oomycetes, viruses, viroids and nematodes. For agricultural production, plant cultivars should therefore exhibit acceptable levels of resistance to a spectrum of pathogens to prevent economic yield losses. Indeed, crop varieties showing multiple disease resistance have been developed through phenotypic selection. This raises a fundamental question: do single loci with pleiotropic effects on multiple diseases contribute to that spectrum of resistance?

Various lines of evidence support the existence of multiple-disease-resistance genes in plants. Several studies, mostly conducted using induced mutants and transformants of *Arabidopsis*, have implicated specific genes that condition multiple disease resistance (e.g. *NON-RACE-SPECIFIC DISEASE RESISTANCE 1* [*NDR1*] [71], *NON-EXPRESSION OF PR 1* [*NPR1*] [72], *cir1, 2 and 3* [73], *enhanced susceptibility to Alternaria* [*esa1*] [74], *WRKY33* [53], and *ASYMMETRIC LEAVES1* [*AS1*] [75]). In several of these studies, multiple-disease-resistance genes were reported to be effective against one group of pathogens (e.g. biotrophs), while increasing the susceptibility of the plant to another group (e.g. necrotrophs). Currently, it is not known whether these genes contribute to a natural variation in resistance that could be manipulated by selection.

Further evidence for multiple-disease-resistance genes based on quantitative genetic analysis comes in several forms. Phenotypic and genetic correlations for resistance to different pathogens have been documented in various populations (e.g. Refs [76,77]). In populations under selection for QDR, correlated reductions in diseases for which resistance was not specifically selected have also been reported [78]. QRL-mapping studies for disease resistance have shown that QRLs for different diseases often colocalize, and clusters of QRLs for multiple diseases have been observed in summaries of QRL-mapping studies [46,79]. For some colocalizing QRLs in rice, the same parent contributed resistance to multiple diseases [46]. The resolution of these studies, however, does not permit pleiotropy to be distinguished from linkage, limiting inference about quantitative variation in multiple–disease-resistance genes. Using a collection of diverse maize inbred lines with gene-level linkage disequilibrium (a determinant of mapping resolution) [80], significant positive genetic correlations were found for resistance to three different foliar fungal pathogens (R. Wisser *et al.*, unpubished observations), suggesting the existence of functionally variable multiple-disease-resistance genes.

plants deploy against pathogens. It is reasonable to expect that these types of compound are components of QDR. After QRL mapping in the *Arabidopsis–Botrytis* pathosystem [25], biochemical studies showed that levels of camalexin (a phytoalexin) were correlated with QDR, and that camalexin sensitivity of different pathogen isolates contributed to isolate specificity [43]. Although this evidence is only correlative, it suggests that genes controlling phytoalexin levels underlie QRLs.

The results of several studies using phytoalexin-deficient mutants (e.g. *pad2-1* and *pad3-1*; [44]) have suggested that reduced amounts of glutathione was the cause of susceptibility to several pathogens [45]. Additional evidence connecting quantitative variation in host resistance to glutathione-mediated mechanisms was found in a bioinformatic analysis of rice, in which members of the glutathione *S*-transferase (GST) gene family were found to colocalize with QRLs [46]. GSTs have been implicated in diverse functions, and their cytoprotective roles during plant–pathogen interactions are well documented (e.g. Refs [47–49]).

Necrotrophic pathogens use numerous secondary metabolites to disrupt normal cell processes, trigger host cell death and destroy host tissue. The well-studied pathogen *Botrytis cinerea* uses an arsenal of compounds to attack its hosts. Botrydial, a phytotoxin, has been shown to be a virulence factor [50]. Likewise, production of oxalic acid is a potent weapon for *B. cinerea*, causing a reduction in host oxidative burst and defense responses, as well as producing an acidic environment for further enzymatic degradation [51]. It has been shown that oxalate oxidase in the host can mitigate damage caused by pathogen-produced oxalic acid [52]. Thus, the mode of necrotrophic pathogen attack naturally implicates toxin production and mitigation in QDR.

Hypothesis #4. QRLs are involved in defense signal transduction

To modulate induced defense responses, plants have developed a complex system for the effective transmission of signals from initial pathogen perception to the activation of defense mechanisms. This often involves matching the defense response to the respective invader (e.g. biotrophic versus necrotrophic pathogen versus herbivore) and uses the phytohormones salicylic acid (SA), jasmonic acid (JA) and ethylene (ET). Different alleles of genes involved in the regulation of these signaling pathways might be QRLs. For example, mutant alleles of the transcription factor *WRKY33* increased susceptibility to the necrotrophic pathogen *B. cinerea* in *Arabidopsis* [53]. Similarly, mutations in the *Arabidopsis* signaling component MAP kinase 4 (*MPK4*) resulted in heightened resistance to *Pseudomonas syringe* pv. *tomato* and *Peronospora parasitica* [54]. There are numerous other examples of signaling components that condition varying levels of increased susceptibility or resistance when mutated (e.g. Refs [55,56]). Often, these signaling mutations increase resistance to a range of similar pathogens (i.e. biotrophs) but increase susceptibility to other pathogens (i.e. necrotrophs) and could also contribute to the broad spectrum resistance of some QRLs (Box 1).

Hypothesis #5. QRLs are weak forms of R-genes

Several authors have posited that QRLs are simply weaker forms of R-genes [2]. There are several compelling lines of evidence that allelic variants at R-genes account for a proportion of QDR in plants. Colocalization of QRLs and R-genes has been noted in several species, including rice [57], maize [58], and potato [59]. In rice, both R-genes and R-gene analogs (RGAs; see Glossary) were significantly associated with QRLs [46].

Although dogma has it that R-genes confer complete race-specific resistance and QRLs confer partial race non-specific resistance, this is often not the case. There are numerous examples of R-genes that condition incomplete resistance, including several that have been cloned and identified as NB-LRR genes. A catalytically impaired mutant of the R-gene *Xa21* confers partial rice blast resistance [4]. Other examples include genes from the maize common rust, flax rust, potato late blight and tomato leaf mold systems [60–63]. Likewise, many QRLs have been shown to be isolate- or race-specific (Box 2). *Resistance to Colletotrichum graminicola 1* (*Rcg1*), a large-effect QRL for resistance to anthracnose stalk rot, has been isolated by map-based cloning and found to encode an NB-LRR resist-

Box 2. Narrow-spectrum QRLs: evidence for gene-for-gene interactions in QDR

Although QDR is generally presumed to be non-race-specific (e.g. [1]), several lines of evidence challenge this dogma. Race-specific QRLs have been identified in multiple pathosystems. These include rose blackrot (*Diplocarpon rosae*) [81]; rice blast (*Magnaporthe oryzae*) [82]; leaf rust (*Puccinia hordei*) in barley [83]; vascular wilt (*Fusarium oxysporum*) in melon (*Cucumis melo* L.) [84]; black stem (*Phoma macdonaldii*) in sunflower (*Helianthus annuus*) [85]; and leaf stripe (*Pyrenophora graminea*) in barley [86]. In the rice–*Xanthomonas* pathosystem, for example, Li *et al.* [82] evaluated two mapping populations for resistance to ten different pathogen races and found that numerous QRLs were effective only against a subset of the pathogen races. Even more striking was that, for some of the QRLs, resistance was contributed by one parent for a given race and the other parent for a different race. This study provides clear examples of the race-specificity of QRLs, and the authors speculate that QDR is a weaker form of race-specific (R-gene-mediated) resistance [82].

Pathogen adaption on hosts with partial resistance has also been demonstrated in several pathosystems. A population of *Cochliobolus heterostrophus*, the causal agent of southern leaf blight in maize, was shown to have increased virulence on the specific host genotype on which increased virulence was selected compared with host genotypes on which the pathogen population was not selected [87]. Likewise, isolates of *Phytophthora infestans*, the causal agent of potato late blight, were shown to be more aggressive on the cultivar from which they were isolated [88]. Both of these studies considered cultivars with only QDR, supporting the hypothesis that QRLs condition resistance in a race-specific manner.

This evidence is consistent with the hypothesis that some QRLs condition a weaker form of R-gene-mediated defense, as proposed by Parlevliet and Zadoks [89], although it is also possible that other mechanisms provide isolate-specific resistance (e.g. camalexin sensitivity). In this view, phenotypic variance and durability can be explained by a minor-gene-for-minor-gene interaction, where virulence genes of minor effect in the pathogen correspond to resistance genes of minor effect in the host (QRLs). This is supported by cultivar × isolate interactions and/or race specificity of QRLs [90]. A rice blast QRL, *Pi34*, and a corresponding avirulence (aggressiveness) gene, *AVR-Pi34*, have been shown to interact in a typical gene-for-gene manner, giving further credibility to the idea of this type of minor interaction [91].

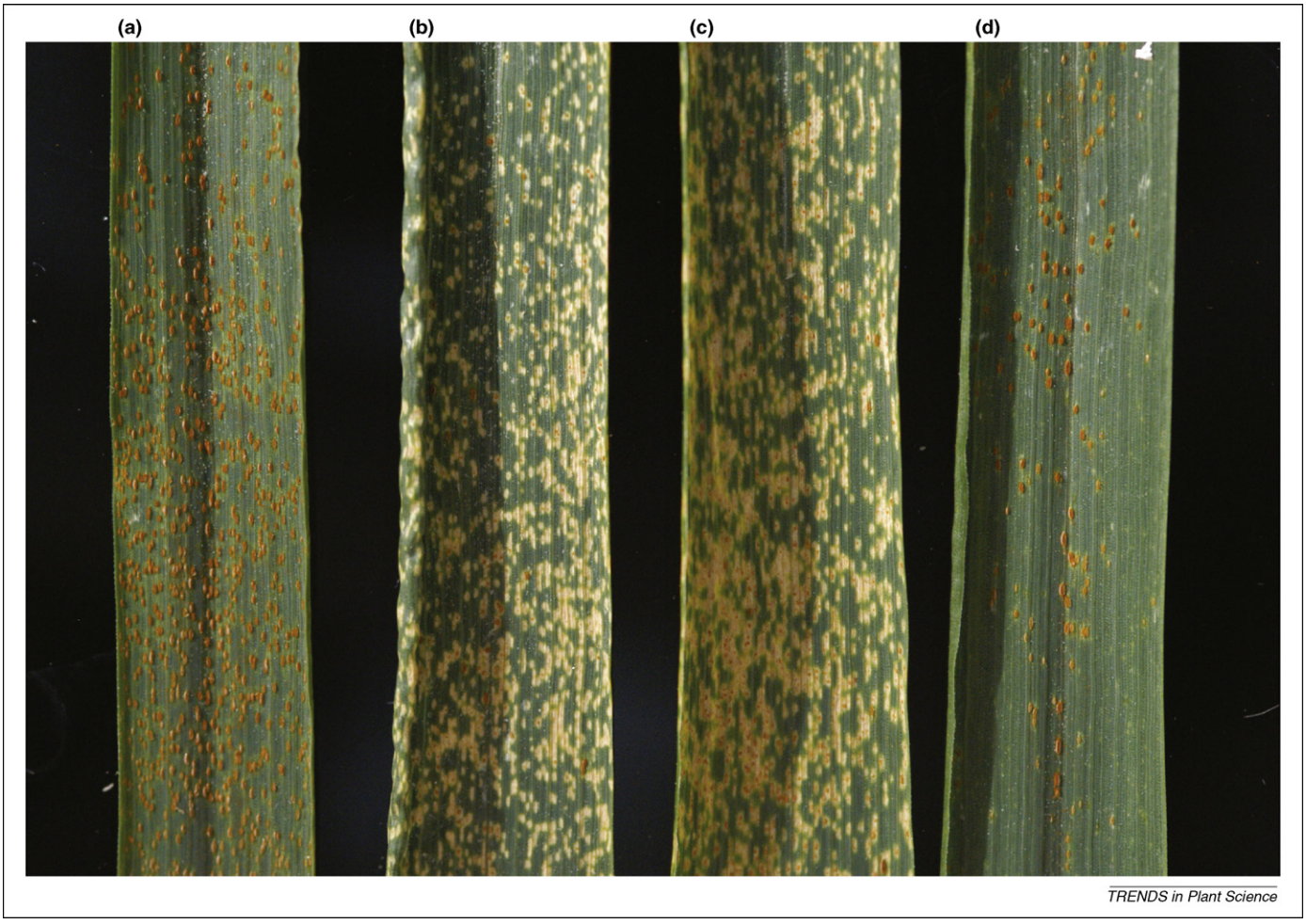

Figure 2. Different reaction types associated with R-genes in the wheat leaf rust pathosystem (causal agent, *Puccinia triticina*). **(a)** Thatcher (susceptible); **(b)** Thatcher + *Lr12* (resistant); **(c)** Thatcher + *Lr13* (resistant); and **(d)** Thatcher + *Lr34* (resistant). The typical susceptible reaction of Thatcher is characterized by numerous uredinial pustules producing rust-colored spores. The resistance genes *Lr12* and *Lr13* are characterized by a hypersensitive response (HR) that eliminates pathogen growth in an incompatible reaction. The resistance gene *Lr34* is not characterized by HR, but rather a reduction in disease severity. Although *Lr34* can be distinguished as a single gene in a segregating population, lines carrying *Lr34* are compatible with *P. triticina* and do not show race specificity. *Lr34* tends to act as a large-effect QRL, blurring the distinction between R-genes and QRLs. Reproduced with permission from James Kolmer.

ance gene [64]. Although not known to be race specific, *Rcg1* illustrates the largely semantic distinction between R-genes and some QRLs.

Thus, qualitative and quantitative disease resistance might only be two ends of a continuum, with R-genes tending to lie toward one end of the spectrum and QRLs toward the other (Figure 2). Although selection favors R-genes with strong effects, pathogen evolution can erode the effectiveness of R-genes, converting them into QRLs. It has been observed that when a pathogen strain overcomes an R-gene, the level of disease in the presence of the 'defeated' R-gene (see Glossary) is sometimes reduced relative to the level of disease in the absence of the R allele. This phenomenon, known as 'residual resistance' is seen for the *Xa4* R-gene in the rice–*Xanthomonas oryzae* pv. *oryzae* system [65] and also in the wheat stem rust [66] and powdery mildew [67] pathosystems.

Hypothesis #6. QRLs are a unique set of previously unidentified genes

There are two published reports on QDR in rice providing evidence that QRLs represent classes of genes not previously reported to function in disease resistance. A QRL for rice blast, *pi21*, has been isolated by map-based cloning. It was found to be a proline-rich gene of unknown function that lacks similarity to any currently known defense-related genes (Ref. [68], S. Fukuoka, personal communication). A second QRL conditioning resistance to rice blast, *Pi34*, has been narrowed to a 65-kb region containing ten predicted open reading frames [5]. None of these candidate genes have sequence similarity to any previously reported defense genes.

The next frontier

Over the past several years, a detailed model of the gene-for-gene type of plant–pathogen interactions has emerged involving recognition, evasion and defense [13]. Many facets of this model can be invoked as potential mechanisms of QDR, including variation in basal resistance, weak R-gene-mediated responses, differences in the speed and effectiveness of the defense response once the pathogen has been detected and even variable sensitivity to suppression of the defense responses by effectors. However, it appears probable that the molecular basis of QDR will draw upon an even broader mechanistic base. Aspects such as plant morphology and development, components of signal

transduction systems, antimicrobial compounds such as phytoalexins, and other, as-yet unknown factors are also likely to be important components of QDR. There is evidence that QDR is conditioned by genes previously unassociated with disease resistance that could control a range of morphological, detoxification or developmental pathways in the plant host.

Two exciting frontiers in QDR research will be the further isolation and characterization of QRLs and the phenotypic analysis of QRLs as they affect the developmental biology and biochemistry of host–pathogen interactions. Cloning additional genes underlying QRLs and determining their functions will reveal the ways in which QRLs contribute to plant defense. This knowledge will enable more efficient and effective utilization of these genes in crop improvement and protection. New genomic platforms in crop species, such as a nested association mapping population of maize, are providing unprecedented power for discovery and characterization of quantitative trait loci (QTLs, see Glossary) [69]. With growing community resources, such as public recombinant inbred line populations (see Glossary) and development of genome-wide association platforms, a greater focus on QDR in *Arabidopsis* could lead to additional advances in our understanding of this important agricultural and biological phenomenon.

The power of detailed observation will complement these genomic advances because careful phenotypic characterization will be essential to understanding these genes of modest effects. Analysis under natural conditions will be an important consideration for distinguishing minor phenotypic differences (e.g. Ref. [37]). Valuable insights are being gained from observations on the resistance phenotypes (macroscopic and microscopic) associated with QRLs in mapping populations and near isogenic lines (see Glossary). For example, characterization of QDR in the cereal rusts indicates that QRLs often act at the level of the cell wall, reducing the efficiency with which the biotrophic fungi enter the cell [70]. An understanding of the developmental processes associated with pathogenesis, as well as the microscopic phenotypes associated with failure or attenuation of pathogenesis on resistant hosts, can provide important clues to the mechanisms of resistance. Current genomic advances situate QDR as an exciting field for systems biology research with the additional prospect of valuable applications in crop improvement.

Acknowledgements

We appreciate helpful comments from Seth Murray. Funding was provided by the CGIAR Generation Challenge Program, the McKnight Foundation, Cornell University, the United States Department of Agriculture (USDA) Agricultural Research Service (ARS), the USDA National Research Initiative and the North Carolina Corn Growers Association.

References

1 van der Plank, J.E. (1968) *Disease Resistance in Plants.* Academic Press
2 Young, N.D. (1996) QTL mapping and quantitative disease resistance in plants. *Annu. Rev. Phytopathol.* 34, 479–501
3 Kamoun, S. *et al.* (1999) Resistance to oomycetes: a general role for the hypersensitive response? *Trends Plant Sci.* 4, 196–200
4 Andaya, C.B. and Ronald, P.C. (2003) A catalytically impaired mutant of the rice *Xa21* receptor kinase confers partial resistance to *Xanthomonas oryzae* pv *oryzae*. *Physiol. Mol. Plant Pathol.* 62, 203–208
5 Zenbayashi-Sawata, K. *et al.* (2007) Genetic and physical mapping of the partial resistance gene, *pi34*, to blast in rice. *Phytopathology* 97, 598–602
6 Liu, B. *et al.* (2004) Candidate defense genes as predictors of quantitative blast resistance in rice. *Mol. Plant Microbe Interact.* 17, 1146–1152
7 Wang, Z. *et al.* (2001) Rice ESTs with disease-resistance gene- or defense-response gene-like sequences mapped to regions containing major resistance genes or QTLs. *Mol. Genet. Genomics* 265, 302–310
8 McDonald, B.A. and Linde, C. (2002) Pathogen population genetics, evolutionary potential, and durable resistance. *Annu. Rev. Phytopathol.* 40, 349–379
9 Stokstad, E. (2007) Deadly wheat fungus threatens world's breadbaskets. *Science* 315, 1786–1787
10 Ayliffe, M. *et al.* (2008) Durable resistance to wheat stem rust needed. *Curr. Opin. Plant Biol.* 11, 187–192
11 Landeo, J. *et al.* (1995) Breeding for horizontal resistance to late blight in potato free of R-genes. In *Phytophthora infestans* (Dowley, L. *et al.*, eds), pp. 268–274, Bole Press Ltd
12 Bent, A.F. and Mackey, D. (2007) Elicitors, effectors, and R genes: the new paradigm and a lifetime supply of questions. *Annu. Rev. Phytopathol.* 45, 399–436
13 Nimchuk, Z. *et al.* (2003) Recognition and response in the plant immune system. *Annu. Rev. Genet.* 37, 579–609
14 Jones, J.D.G. and Dangl, J.L. (2006) The plant immune system. *Nature* 444, 323–329
15 Johal, G.S. and Briggs, S.P. (1992) Reductase activity encoded by the *Hm1* disease resistance gene in maize. *Science* 258, 985–987
16 Büschges, R. *et al.* (1997) The barley *mlo* gene: a novel control element of plant pathogen resistance. *Cell* 88, 695–705
17 Romer, P. *et al.* (2007) Plant pathogen recognition mediated by promoter activation of the pepper *bs3* resistance gene. *Science* 318, 645–648
18 Nagy, E.D. *et al.* (2007) Fine mapping of the *Pc* locus of *Sorghum bicolor*, a gene controlling the reaction to a fungal pathogen and its host-selective toxin. *Theor. Appl. Genet.* 114, 961–970
19 Lorang, J.M. *et al.* (2007) Plant disease susceptibility conferred by a 'resistance' gene. *Proc. Natl. Acad. Sci. U. S. A.* 104, 14861–14866
20 Sindhu, A. *et al.* (2008) A guardian of grasses: specific origin and conservation of a unique disease-resistance gene in the grass lineage. *Proc. Natl. Acad. Sci. U. S. A.* 105, 1762–1767
21 Brandwagt, B.F. *et al.* (2002) Overexpression of the tomato *Asc-1* gene mediates high insensitivity to AAL toxins and fumonisin B1 in tomato hairy roots and confers resistance to *Alternaria alternata* f. Sp. *Lycopersici* in *Nicotiana umbratica* plants. *Mol. Plant Microbe Interact.* 15, 35–42
22 Balint-Kurti, P.J. *et al.* (2008) Identification of quantitative trait loci for resistance to southern leaf blight and days to anthesis in two maize recombinant inbred line populations. *Phytopathology* 98, 315–320
23 Kover, P.X. and Schaal, B.A. (2002) Genetic variation for disease resistance and tolerance among *Arabidopsis thaliana* accessions. *Proc. Natl. Acad. Sci. U. S. A.* 99, 11270–11274
24 Wilson, I.W. *et al.* (2001) Quantitative trait loci analysis of powdery mildew disease resistance in the *Arabidopsis thaliana* accession Kashmir-1. *Genetics* 158, 1301–1309
25 Denby, K.J. *et al.* (2004) Identification of *Botrytis cinerea* susceptibility loci in *Arabidopsis thaliana*. *Plant J.* 38, 473–486
26 Singh, R.P. *et al.* (2005) Genetics and breeding for durable resistance to leaf and stripe rusts in wheat. *Turk. J. Agric. For.* 29, 121–127
27 Parlevliet, J. (2002) Durability of resistance against fungal, bacterial and viral pathogens; present situation. *Euphytica* 124, 147–156
28 Hu, G. *et al.* (1997) Adult plant phenotype of the *Rp1–DJ* compound rust resistance gene in maize. *Phytopathology* 87, 236–241
29 Penning, B.W. *et al.* (2004) A major suppressor of cell death, *slm1*, modifies the expression of the maize (*Zea mays* l.) lesion mimic mutation *les23*. *Genome* 47, 961–969
30 Collins, A. *et al.* (1999) QTL for field resistance to late blight in potato are strongly correlated with maturity and vigour. *Mol. Breed.* 5, 387–398
31 Steffenson, B.J. *et al.* (1996) Genetics of seedling and adult plant resistance to net blotch (*Pyrenophora teres f. Teres*) and spot blotch (*Cochliobolus sativus*) in barley. *Theor. Appl. Genet.* 92, 552–558

32 Thompson, D.L. and Bergquist, R.R. (1984) Inheritance of mature plant resistance to *Helminthosporium maydis* race 0 in maize. *Crop Sci.* 24, 807–811
33 Melotto, M. *et al.* (2006) Plant stomata function in innate immunity against bacterial invasion. *Cell* 126, 969–980
34 Bradley, D.J. *et al.* (2003) Susceptibility of clover species to fungal infection: the interaction of leaf surface traits and environment. *Am. J. Bot.* 90, 857–864
35 Albar, L. *et al.* (1998) Genetic basis and mapping of the resistance to rice yellow mottle virus. I. QTLs identification and relationship between resistance and plant morphology. *Theor. Appl. Genet.* 97, 1145–1154
36 Zhu, H. *et al.* (1999) Does function follow form? Principal QTLs for fusarium head blight (FHB) resistance are coincident with QTLs for inflorescence traits and plant height in a doubled-haploid population of barley. *Theor. Appl. Genet.* 99, 1221–1232
37 Zipfel, C. *et al.* (2004) Bacterial disease resistance in *Arabidopsis* through flagellin perception. *Nature* 428, 764–767
38 Dunning, F.M. *et al.* (2007) Identification and mutational analysis of *Arabidopsis FLS2* leucine-rich repeat domain residues that contribute to flagellin perception. *Plant Cell* 19, 3297–3313
39 Shibuya, N. and Minami, E. (2001) Oligosaccharide signaling for defense responses in plants. *Physiol. Mol. Plant Pathol.* 59, 223–233
40 Miya, A. *et al.* (2007) *CERK1*, a LysM receptor kinase, is essential for chitin elicitor signaling in *Arabidopsis*. *Proc. Natl. Acad. Sci. U. S. A.* 104, 19613–19618
41 Ramonell, K. *et al.* (2005) Loss-of-function mutations in chitin responsive genes show increased susceptibility to the powdery mildew pathogen *Erysiphe cichoracearum*. *Plant Physiol.* 138, 1027–1036
42 Wan, J. *et al.* (2008) A LysM receptor-like kinase plays a critical role in chitin signaling and fungal resistance in *Arabidopsis*. *Plant Cell* 20, 471–481
43 Kliebenstein, D.J. *et al.* (2005) Secondary metabolites influence *Arabidopsis*/*Botrytis* interactions: variation in host production and pathogen sensitivity. *Plant J.* 44, 25–36
44 Roetschi, A. *et al.* (2001) Characterization of an *Arabidopsis–Phytophthora* pathosystem: resistance requires a functional *Pad2* gene and is independent of salicylic acid, ethylene and jasmonic acid signalling. *Plant J.* 28, 293–305
45 Parisy, V. *et al.* (2007) Identification of *pad2* as a γ-glutamylcysteine synthetase highlights the importance of glutathione in disease resistance of *Arabidopsis*. *Plant J.* 49, 159–172
46 Wisser, R.J. *et al.* (2005) Identification and characterization of regions of the rice genome associated with broad-spectrum, quantitative disease resistance. *Genetics* 169, 2277–2293
47 Dean, J.D. *et al.* (2005) Induction of glutathione s-transferase genes of *Nicotiana benthamiana* following infection by *Colletotrichum destructivum* and *C. orbiculare* and involvement of one in resistance. *J. Exp. Bot.* 56, 1525–1533
48 Marrs, K.A. (1996) The functions and regulation of glutathione s-transferases in plants. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* 47, 127–158
49 Schlaeppi, K. *et al.* (2008) The glutathione-deficient mutant *pad2-1* accumulates lower amounts of glucosinolates and is more susceptible to the insect herbivore *Spodoptera littoralis*. *Plant J.* 55, 774–786
50 Colmenares, A.J. *et al.* (2002) The putative role of botrydial and related metabolites in the infection mechanism of *Botrytis cinerea*. *J. Chem. Ecol.* 28, 997–1005
51 van Kan, J.A.L. (2006) Licensed to kill: the lifestyle of a necrotrophic plant pathogen. *Trends Plant Sci.* 11, 247–253
52 Walz, A. *et al.* (2008) Expression of an oxalate oxidase gene in tomato and severity of disease caused by *Botrytis cinerea* and *Sclerotinia sclerotiorum*. *Plant Pathol.* 57, 453–458
53 Zheng, Z. *et al.* (2006) *Arabidopsis WRKY33* transcription factor is required for resistance to necrotrophic fungal pathogens. *Plant J.* 48, 592–605
54 Petersen, M. *et al.* (2000) *Arabidopsis* MAP kinase 4 negatively regulates systemic acquired resistance. *Cell* 103, 1111–1120
55 Koornneef, A. and Pieterse, C.M.J. (2008) Cross talk in defense signaling. *Plant Physiol.* 146, 839–844
56 Kunkel, B.N. and Brooks, D.M. (2002) Cross talk between signaling pathways in pathogen defense. *Curr. Opin. Plant Biol.* 5, 325–331
57 Wang, G.L. *et al.* (1994) *RFLP* mapping of genes conferring complete and partial resistance to blast in a durably resistant rice cultivar. *Genetics* 136, 1421–1434
58 Xiao, W. *et al.* (2007) Mapping of genome-wide resistance gene analogs (RGAs) in maize (*Zea mays* l.). *Theor. Appl. Genet.* 115, 501–508
59 Gebhardt, C. and Valkonen, J.P.T. (2001) Organization of genes controlling disease resistance in the potato genome. *Annu. Rev. Phytopathol.* 39, 79–102
60 Smith, S.M. and Hulbert, S.H. (2005) Recombination events generating a novel *Rp1* race specificity. *Mol. Plant Microbe Interact.* 18, 220–228
61 Parniske, M. *et al.* (1997) Novel disease resistance specificities result from sequence exchange between tandemly repeated genes at the Cf-4/9 locus of tomato. *Cell* 91, 821–832
62 Lawrence, G.J. *et al.* (1995) The l6 gene for flax rust resistance is related to the *Arabidopsis* bacterial resistance gene *RPS2* and the tobacco viral resistance gene *N*. *Plant Cell* 7, 1195–1206
63 Stewart, H.E. *et al.* (2003) The effect of the presence of R-genes for resistance to late blight (*Phytophthora infestans*) of potato (*Solanum tuberosum*) on the underlying level of field resistance. *Plant Pathol.* 52, 193–198
64 Broglie, K.E. *et al.* E.I. du Pont de Nemours and Company, Pioneer Hi-Bred International, Inc.; University of Delaware. Polynucleotides and methods for making plants resistant to fungal pathogens, United States Patent 20060223102
65 Li, Z.K. *et al.* (1999) A 'defeated' rice resistance gene acts as a QTL against a virulent strain of *Xanthomonas oryzae* pv. *Mol. Gen. Genet.* 261, 58–63
66 Brodny, U. *et al.* (1986) Residual and interactive expressions of 'defeated' wheat stem rust resistance genes. *Phytopathology* 76, 546–549
67 Nass, H.A. *et al.* (1981) The residual effects of some defeated powdery mildew *Erysiphe-graminis-f-sp-tritici* resistance genes in isolines of winter wheat. *Phytopathology* 71, 1315–1318
68 Fukuoka, S. *et al.* National Institute of Agrobiological Sciences, Japan. Rice blast disease gene *Pi21*, resistance gene *pi21* and utilization thereof, World Intellectual Property Organization Patient WO/2007/000880
69 Yu, J. *et al.* (2008) Genetic design and statistical power of nested association mapping in maize. *Genetics* 178, 539–551
70 Collins, N.C. *et al.* (2007) Resistance to cereal rusts at the plant cell wall – what can we learn from other host–pathogen systems? *Aust. J. Agric. Res.* 58, 476–489
71 Century, K.S. *et al.* (1997) *NDR1*, a pathogen-induced component required for *Arabidopsis* disease resistance. *Science* 278, 1963–1965
72 Mou, Z. *et al.* (2003) Inducers of plant systemic acquired resistance regulate *NPR1* function through redox changes. *Cell* 113, 935–944
73 Murray, S.L. *et al.* (2005) A constitutive *PR-1::luciferase* expression screen identifies *Arabidopsis* mutants with differential disease resistance to both biotrophic and necrotrophic pathogens. *Mol. Plant Pathol.* 6, 31–41
74 Tierens, K.F.M.J. *et al.* (2002) *Esa1*, an *Arabidopsis* mutant with enhanced susceptibility to a range of necrotrophic fungal pathogens, shows a distorted induction of defense responses by reactive oxygen generating compounds. *Plant J.* 29, 131–140
75 Nurmberg, P.L. *et al.* (2007) The developmental selector *As1* is an evolutionarily conserved regulator of the plant immune response. *Proc. Natl. Acad. Sci. U. S. A.* 104, 18795–18800
76 Hill, R.R. and Leath, K.T. (1975) Genotypic and phenotypic correlations for reaction to five foliar pathogens in alfalfa. *Theor. Appl. Genet.* 45, 254–258
77 Mitchell-Olds, T. *et al.* (1995) Genetics of *Brassica rapa* (syn. *Campestris*). 2. Multiple disease resistance to three fungal pathogens: *Peronospora parasitica, Albugo candida* and *Leptosphaeria maculans*. *Heredity* 75, 362–369
78 Lambert, R.J. and White, D.G. (1997) Disease reaction changes from tandem selection for multiple disease resistance in two maize synthetics. *Crop Sci.* 37, 66–69
79 Wisser, R.J. *et al.* (2006) The genetic architecture of disease resistance in maize: a synthesis of published studies. *Phytopathology* 96, 120–129
80 Flint-Garcia, S.A. *et al.* (2005) Maize association population: a high-resolution platform for quantitative trait locus dissection. *Plant J.* 44, 1054–1064
81 Whitaker, V.M. *et al.* (2007) Resistance of 12 rose genotypes to 14 isolates of *Diplocarpon rosae* wolf (rose blackspot) collected from eastern North America. *Plant Breed.* 126, 83–88

82 Li, Z.K. *et al.* (2006) Complex genetic networks underlying the defensive system of rice (*Oryza sativa* l.) to *Xanthomonas oryzae* pv. *Proc. Natl. Acad. Sci. U.S.A.* 103, 7994–7999
83 Parlevliet, J.E. (1978) Race-specific aspects of polygenic resistance of barley to leaf rust, *Puccinia hordei*. *Eur. J. Plant Pathol.* 84, 121–126
84 Perchepied, L. *et al.* (2005) Strain-specific and recessive QTLs involved in the control of partial resistance to *Fusarium oxysporum* f. Sp. *Melonis* race 1.2 in a recombinant inbred line population of melon. *Theor. Appl. Genet.* 111, 65–74
85 Darvishzadeh, R. *et al.* (2007) Quantitative trait loci associated with isolate specific and isolate nonspecific partial resistance to *Phoma macdonaldii* in sunflower. *Plant Pathol.* 56, 855–861
86 Arru, L. *et al.* (2003) Isolate-specific QTLs of resistance to leaf stripe (*Pyrenophora graminea*) in the 'Steptoe' × 'Morex' spring barley cross. *Theor. Appl. Genet.* 106, 668–675
87 Kolmer, J.A. and Leonard, K.L. (1986) Genetic selection and adaptation of *Cochliobolus heterostrophus* to corn hosts with partial resistance. *Phytopathology* 76, 774–777
88 Bjor, T. and Mulelid, K. (1991) Differential resistance to tuber late blight in potato cultivars without R-genes. *Potato Res.* 34, 3–8
89 Parlevliet, J.E. and Zadoks, J.C. (1977) The integrated concept of disease resistance: a new view including horizontal and vertical resistance in plants. *Euphytica* 26, 5–21
90 Marcel, T.C. *et al.* (2008) Isolate specificity of quantitative trait loci for partial resistance of barley to *Puccinia hordei* confirmed in mapping populations and near-isogenic lines. *New Phytol.* 177, 743–755
91 Zenbayashi-Sawata, K. *et al.* (2005) *Pi34–AvrPi34*: a new gene-for-gene interaction for partial resistance in rice to blast caused by *Magnaporthe grisea*. *J. Gen. Plant Pathol.* 71, 395–401